Rejection under 35 U.S.C. 103

The Final Office Action, dated February 23, 2004, rejects pending claims 1-3, 5-8, and 13-25 under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,962,246 ("the Ladner patent") in view of Beck (Adv. Exp. Med. Biol. 195:97-104). Applicants traverse.

Standard for Obviousness

The four factual inquiries for determining obviousness were established in *Graham v. John Deere*, 383 U. S. 1, 148 USPQ 459 (1966): First, the scope and content of the prior art must be established. Second, the differences between the prior art and claims at issue must be ascertained. Third, the level of ordinary skill in the art must be resolved. Finally, evidence of secondary considerations is evaluated.

The three criteria for establishing a *prima facie* case of obviousness are set forth in M.P.E.P. §2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Disclosure of the Ladner Patent

The Ladner patent discloses the use of dUTPase as an improved proliferation marker for providing information about the status of a cell (column 3, lines 28-32). Measurement of dUTPase levels can be used to analyze cell proliferation and susceptibility of a cell to therapeutic agents, and to test various therapeutic agents for their ability to inhibit dUTPase (column 3, line 56 – column 4, line 12). The Ladner patent discloses that dUTPase levels are high in proliferating cells and low in non-proliferating cells (column 4, lines 43-45; column 9, line 64 – column 10, line 4). The Ladner patent also discloses that cells with high dUTPase levels are likely to be resistant to anticancer therapy, while cells with low dUTPase levels are likely to be susceptible to such therapies (column 4, line 65 – column 5, line 3; column 9, lines 17-22).

The Ladner patent further discloses a method of determining dUTPase levels in a cell comprising 1) removing the cell, 2) labeling dUTPase in the cell, 3) measuring the amount of dUTPase in the cell, and 4) comparing the amount of dUTPase to that of a control cell with known proliferation status (column 9, lines 53-59; column 10, lines 7-12). The Ladner patent discloses the use of this method to determine the proliferative status of a cell and to evaluate the likely effectiveness of a cancer drug (column 12, lines 32-39).

The Ladner Patent Disclosure Does Not Teach or Suggest the Specific Method of Determining Whether a Test Compound Induces Uracil Misincorporation into DNA of Cells by Inhibiting Thymidylate Metabolism.

The Office Action states that Ladner discloses "a method of claims 1, 13, 22, and 23, for determining if a test compound induces uracil misincorporation into DNA." Essentially, the Office Action attempts to take different portions of the Ladner patent and make them match the claim elements of the present invention. The Ladner patent, while broad, does not teach or suggest the specific claims of the present invention, and in fact, teaches away in some respects.

The Ladner patent states that dUTPase is an ideal proliferation marker because its two isoforms are readily distinguishable, unlike "uracil-DNA glycosylase, which exists in at least six isoforms, some of which are produced irrespectively of the cell cycle" (column 5, lines 41-48). By making this statement, the Ladner patent impliedly teaches away from the use of uracil-DNA glycosylase as a marker by suggesting that it would be too complicated because of its multiple isoforms. A person of skill in the art reading the Ladner patent would not be motivated to combine dUTPase and uracil-DNA glycosylase as proliferation markers, because the Ladner patent suggests a small likelihood of success.

On page 3, the Office Action states: "...wherein presence or absence of uracil in DNA in each of the cell types is indicative of...involvement of dUTPase in cell cycle checkpoint arrest (cyclin dependent kinase phosphorylation)." First, the Ladner patent, while broad, does not disclose the measurement of uracil incorporation into DNA. Second, the Ladner patent does not discuss why the presence or absence of uracil in DNA would indicate involvement of dUTPase in cell cycle checkpoint arrest. The Ladner patent discloses that both the DUT-M and DUT-N

isoforms of dUTPase contain a consensus target sequence for the cyclin dependent protein kinase $p34^{cdc2}$, and that the DUT-N is phosphorylated at this position (column 8, lines 5-7 and 50-54). The Ladner patent also discloses that phosphorylation of dUTPase increases during cell proliferation (column 2, lines 8-11). However, it does not elucidate the role of dUTPase in cell cycle control. The Ladner patent also does not attempt to define, as the present invention has, the specific cell cycle checkpoints associated with aberrant uracil-DNA metabolism.

Contrary to the statements in the Office Action, the Ladner patent, while broad, does not teach a method for "determining if a test compound induces uracil misincorporation into DNA" or "measuring cell growth or proliferation or viability or measuring incorporation of uracil (dUTP)." The Ladner patent discloses the measurement of dUTPase levels only.

Thus, the Ladner patent does not render the present invention obvious because it fails to teach or suggest key aspects of the present invention.

Disclosure of the Beck Reference

Beck discloses that cell lines with low dUTPase levels are less susceptible to uracil misincorporation in the presence of methotrexate (MTX), while cell lines with high dUTPase levels are more susceptible (Figure 2). Beck tested a variety of uracil analogues for their effect on dUTPase levels, and found that those analogues that inhibited dUTPase also increased the cytotoxicity of MTX (Figure 5; Table 3).

The Beck Reference Discloses the Use of dUPTase Measurements Only, Which Does Not Make the Present Invention Obvious

Page 4 of the Office Action states that Beck discloses "a method for screening cytotoxic agent (methotrexate) and uracil analogues that affect uracil misincorporation." According to the Office Action, this method comprises the following steps: i) "assaying the dUTPase and uracil-DNA glycosylase (UNG) levels in various cell lines," ii) "correlating test compound resistance with dUTPase levels by analyzing dUTPase, UGN, cell growth and uracil misincorporation...and implicating that the inhibition of dUTPase activity elevates dUTP levels and enhance

misincorporation of uracil into DNA and cytotoxicity." The Office Action also states that Beck discloses "that the method comprises inhibitor of uracil-DNA glycosylase."

The Office Action overstates the scope of the disclosure in Beck. First, the statement that the method in Beck "comprises inhibitor of uracil-DNA glycosylase" is incorrect. Beck assayed a variety of cell lines for uracil-DNA glycosylase activity, and found that activity varied widely (Fig. 1, middle panel). Beck also observed that uracil-DNA glycosylase activity was inhibited in the presence of uracil (Fig. 1, right panel). However, Beck clearly did not measure or contemplate measuring uracil-DNA glycosylase activity as a method for testing the effectiveness of an anticancer compound. The effect of each uracil analogue on uracil-DNA glycosylase activity was tested, but only so that those analogs affecting uracil-DNA glycosylase activity could be removed from further study (page 101, line 13).

The purpose of Beck was to determine the correlation between dUTPase levels and MTX cytotoxicity, and to determine whether dUTPase inhibitors increased MTX cytotoxicity. Rather than teaching the use of both dUTPase and uracil-DNA glycosylase measurements to test an anticancer compound, Beck is teaching the use of dUTPase measurements only. By testing only those inhibitors that had no effect on uracil-DNA glycosylase, Beck focused exclusively on the effect of dUTPase activity, and was in fact teaching away from using both measures simultaneously.

The Ladner Patent and the Beck Reference, When Considered Together, Do Not Render the Present Invention Obvious.

A person of skill in the art reading the disclosure in the Ladner patent and Beck reference would *not* find it obvious, based on these references, to test an anticancer compound using the method disclosed in the present application. The references cited in the Office Action do not teach or suggest all of the claim limitations of the present invention.

The present invention discloses the use of a combination of four cell types to test the efficacy of an anticancer compound: wild type cells, cells overexpressing dUTPase, cells overexpressing uracil-DNA glycosylase, and cell expressing Ugi. Neither of the cited references describes the use of cell types with specific expression characteristics. Rather, the methods

disclosed in the Ladner patent and Beck utilize cells with a variety of dUTPase expression profiles.

Neither reference discloses the use of uracil-DNA glycosylase levels as a means for testing the efficacy of an anticancer compound. As explained above, both references teach away from the use of uracil-DNA glycosylase levels as a variable for testing the efficacy of a compound.

Further, neither reference even mentions the use of Ugi or any other uracil-DNA glycosylase inhibitor, which is an aspect of the independent claim.

Finally, neither reference discloses the specific cell cycle checkpoints involved in uracil-DNA metabolism. Beck makes no reference to the cell cycle. The Ladner patent describes the use of control cell "in which the cell cycle stage...is known" (column 10, lines 7-10). However, the Ladner patent's references to the cell cycle merely refer to whether a cell is proliferating or not. ("Proliferating" cells may refer to any cell that is not quiescent, meaning that a proliferating cell may be in the G1, S, G2, or M stage of the cell cycle.) The Ladner patent states that dUTPase levels are higher in proliferating cells, but it does not correlate dUTPase levels with any specific part of the cell cycle (e.g., G1, S, etc.).

In conclusion, for the reasons that the cited references do not teach the combination of four cell types, do not teach the use of measuring uracil-DNA glycosylase levels, do not teach the use of Ugi or other uracil-DNA glycosylase inhibitor, and do not teach the use of monitoring specific cell cycle checkpoints, the Ladner patent and Beck disclosure cannot render the present invention obvious.

CONCLUSION

In view of the foregoing, it is submitted that the present claims are in condition for allowance. Accordingly, Applicant respectfully requests that a Notice of Allowance be issued.

If any additional fee is due, the Commissioner is authorized to charge such fees to Perkins Coie's Deposit Account No. **50-2586**. If anything can be done to further this application, please contact the undersigned at 310-788-9900.

Respectfully submitted,
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